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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/428,692	CARR ET AL.	
	Examin r	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 24-102* is/are pending in the application.

4a) Of the above claim(s) *34-44,53,56,58,59,75-85,94,97,99 and 100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,24-33,45-52,54,55,57,60-74,86-93,95,96,98,101 and 102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,24-33,45-52,54,55,57-74,86-93,95,96 and 98-102* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14,15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. The Information Disclosure Statement, filed 4/29/02, has been entered into the record.

B. Amendment B, filed 3/15/02, has been entered into the record. Claims 1-23 were pending in the application. Claims 3-23 were cancelled and new claims 24-102 have been added. Claims 24-102 do not add new matter. However, new claims 34-44, 53, 56, 58, 59, 75-85, 94, 97, 99 and 100 are not being examined since they are drawn to a non-elected invention (i.e. delta and kappa opioid receptor binding moieties). Claims 58, 59, 99 and 100 are being withdrawn due to election by original presentation as discussed below. Therefore, claims 1, 2, 24-33, 45-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 are the subject of this Office Action.

C. The Revocation of Previous Powers of Attorney, and Appointment of Attorney under 37 C.F.R. 3.71, filed 2/19/02, has been entered into the record.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Election by Original Presentation

A. Claims 1-23 were pending in the application. Claims 3-23 have been cancelled and new claims 24-102 have been added. Newly submitted claims 58, 59, 99 and 100 (SEQ ID NO:42 and 43) are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: in response to the restriction requirement dated 7/30/01, Applicants elected SEQ ID NO:3 as the opioid receptor binding moiety and SEQ ID NO:21 as the nociceptive receptor binding moiety. The inventions of the elected group (SEQ ID NO:3 and 21) are distinct from that of a Group drawn to SEQ ID NO:42 or 43 because of the following reasons:

They are products which possess characteristic differences in structure and function and each has an independent utility that is distinct for each invention which cannot be exchanged. Originally filed claim 1, from which all originally elected claims, 2-17 depended, recited "A chimeric peptide comprising an opioid receptor binding moiety and a nociceptive receptor binding moiety." However, in amendment B, Applicants amended claim 1 to recite "A chimeric peptide comprising an N-terminal opioid receptor binding moiety and a C-terminal Substance P receptor agonist binding moiety." Along with this amendment to claim 1, Applicants also added claims which introduce SEQ ID NO:42 and 43, which are chimeras of fragments of SEQ ID NO:3 and 21. SEQ ID NO:42 and 43 were not part of the originally

filed claims and, if they were, would have been subject to restriction since SEQ ID NO:42 and 43 are distinct from SEQ ID NO:3 and 21.

Since Applicants have received an action on the merits for the originally presented invention, this invention (SEQ ID NO:3 and 21) has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 58, 59, 99 and 100 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Therefore, claims 1, 2, 24-33, 45-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 are the subject of this Office Action. This original restriction was made **FINAL** on page 2 of the Office Action dated 12/17/01.

3. Claim Objections

A. Claims 1, 2, 24-26, 31, 33, 45-52, 54, 55, 60-67, 72, 74, 86-93, 95, 96, 101 and 102 are objected to since they encompass non-elected subject matter. In Paper No. 8, Applicants were required to elect one mu opioid receptor binding moiety and one nociceptive receptor binding moiety. In Paper No. 11, Applicants elected the mu opioid receptor binding moiety of SEQ ID NO:3 and the nociceptive receptor binding moiety of SEQ ID NO:21. However, new claims 1, 2, 24-26, 31, 33, 45-52, 54, 55, 60-67, 72, 74, 86-93, 95, 96, 101 and 102 recite that the opioid receptor binding moiety can be *other* than a mu opioid receptor binding moiety, such as either a delta opioid receptor binding moiety, or a kappa opioid receptor binding moiety. Furthermore, these claims also recite SEQ ID NOs other than SEQ ID NO:3 and 21. Therefore, these claims will be examined insofar as they read on the elected subject matter. It is required that Applicants amend the claims to remove reference to non-elected subject matter. Claims 27-30, 32, 57, 68-71, 73 and 98 are also objected to since they depend from these claims.

Furthermore, though NOT being objected to at this time, Applicants should be aware that, when the claims are amended to recite only the elected subject matter, claims 28, 33 and 74 will be substantial duplicates of claims 26, 31 and 72, respectively.

B. Claims 25 and 66 are objected to since the syntax could be improved by replacing the phrase "which ligand" with "wherein said ligand." Claims 26-33, 45-52, 54, 55, 67-74, 86-93, 95 and 96 are also objected to since they depend from these claims.

C. Claims 28-33, 67 and 69-74 are objected to since they depend from rejected claims, 24, 25, 27, 65, 66, or 68, for the reasons provided in the below rejection under 35 USC 112, second paragraph, regarding the term "the mu receptor." However, claims 28-33, 67 and 69-74, themselves, are not confusing since they refer opioid receptor agonists, and not specifically to "the mu receptor."

D. Claims 32, 45, 73 and 86 are objected to since the syntax could be improved by inserting a comma between the word "fragment" and "or." Claims 33 and 74 are also objected to since they depend from these claims.

E. Claims 32, 66 and 73 are objected to since the syntax could be improved by inserting the word "an" between the words "or" and "N-terminal derivative."

4. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1, 2, 24-33, 45-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for chimeric peptides comprising an N-terminal opioid receptor binding moiety and a C-terminal Substance P receptor agonist binding moiety wherein the opioid receptor binding moiety is an endogenous mu opioid peptide, or fragment thereof, and the Substance P receptor agonist binding moiety is Substance P, or a fragment thereof, does not reasonably provide enablement for all mu opioid receptor binding moieties, Substance P receptor agonist binding moieties, "**derivatives**" thereof, those which comprise "**at least one non-natural amino acid**," or "**pharmaceutical compositions**" thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

A rejection of previous claims 6-8, 11-13 and 15 under 35 USC 112, first paragraph, regarding the terms "**fragments**" or "**D-amino acid**" was made on pages 2-3 of the Office Action, dated 12/17/01. No rejection will be made regarding the terms "**fragments**" or "**D-amino acid**" in view of Applicants' arguments on pages 19 and 20, respectively, of the response dated 3/15/02, as well as in view of page 9, line 8 to page 11, line 12 of the specification, which define "fragments" and page 5, lines 20-27 and

Tables 1-4 of the specification, which disclose D-amino acids. However, Applicants' arguments regarding the term "derivative" are not found persuasive and will be addressed in the below scope of enablement rejection under 35 USC 112, first paragraph.

Claim 1 recites "a chimeric peptide comprising an N-terminal opioid receptor binding moiety and a C-terminal Substance P receptor agonist binding moiety." Claims 62-65 recite "pharmaceutical compositions" thereof. Claim 2 recites that the peptide induces analgesia in a mammal and claim 24 recites that the opioid receptor binding moiety binds to a mu opioid receptor. Claims 25, 31-33, 45, 49, 57, 66, 72-74, 86, 90 and 98 recite "derivatives" of these receptor binding moieties, or "pharmaceutical compositions" thereof. Claims 60 and 101 recite that these peptides comprise at least one "non-natural amino acid." Claims 61 and 102, which depend from claims 60 and 101, respectively, recite that the peptides comprise at least one "D-amino acid," but may still comprise other "non-natural" amino acids.

Applicants argue on pages 17-21 of the Response of Paper No. 13 that "[t]he standard for enablement is based on the determination of whether the disclosure contains sufficient information regarding the subject matter of the claim as to enable one skilled in the art to make and use the claimed invention" and that the "Applicant is not required to disclose every operable species, but only representative examples, with enough teaching and guidance so as to enable a person of ordinary skill in the art to practice the invention without undue experimentation." Applicants argue that the present disclosure does teach the artisan how to make the claimed chimeras comprising an N-terminal opioid receptor binding moiety (OM) and a C-terminal Substance P (SP) receptor binding moiety (SPM), and that the specification provides examples of starting materials or precursors suitable to construct the chimeric peptides of the invention (e.g. Tables 1-4). They argue that pages 9-13 of the specification teach how to produce these N- and C-terminal derivatives and that page 5, lines 20-27 teaches how to make opioid and SP moieties comprising D-amino acids (Tables 1-4) and that one of ordinary skill in the art could make the claimed chimeric peptides without undue experimentation.

Applicants' arguments have been considered, but are not deemed persuasive. In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Though Applicants are not required to disclose every operable species, only representative examples, with enough teaching and guidance so as to enable a person of ordinary skill in the art to practice the invention without undue experimentation, and that the disclosure is only required to contain sufficient information regarding the subject matter of the claim as to enable one skilled in the art to make and use the claimed invention, Applicants have only provided representative examples, starting materials and sufficient information, to enable the artisan to make and use chimeras comprising the endogenous mu opioid receptor binding moieties of Table I and the SP receptor agonist binding moieties of Table 4. Regarding the term "derivative," the breadth of these claims is excessive. Applicants define "derivatives" of a peptide as a sequence of at least 4 amino acids which specifically recognize an epitope. However, Applicants do not provide any guidance or working examples as to what this epitope is, if this epitope is the same in all of these "derivatives," or if it is a randomly chosen epitope not related to peptide function. Applicants further define these derivatives as molecules other than full-length, and which may be as little as 30% identical to (i) an amino acid sequence of identical size, or (ii) when compared to an aligned sequence, or (iii) when the encoding nucleic acid is capable of hybridizing under even non-stringent conditions to the nucleotide sequences encoding these aforementioned peptides and amino acid sequences (page 10, line 26 to page 11, line 12 of the specification). Furthermore, page 11, lines 13-23 of the specification define derivatives as containing various additions, deletions and substitutions to the original peptide and which result in "functionally equivalent molecules." However, it is not understood what this "function" is, or which amino acid residues are critical to maintain this function. Therefore, the scope of the claims includes any and all peptides which are "derived" from any and all mu opioid receptor ligands, whether endogenous, or exogenous, and which include peptides with only minimal structural and functional requirements as compared to those in Tables 1 and 4 of the specification.

Furthermore, Applicants have not provided sufficient guidance or working examples of any mu opioid peptide binding moieties other than those listed in Table 1 of the specification, said moieties of Table I being based on the structure of endogenous mu opioid binding moieties, or any SP receptor agonist binding moieties other than those in Table 4 of the specification. Regarding the claimed pharmaceutical compositions comprising these moieties, Applicants have not provided any guidance or working examples of C-terminal SP moieties other than those disclosed in Table 4 of the specification, which are based on SP, or of N-terminal mu opioid receptor binding moieties which would retain the necessary biological (i.e. therapeutic) activity other than the class of mu endogenous opioid peptides, including those in Table 1 of the specification, which comprise the Tyr^1 – Phe^4 residues of the N-terminal tetrapeptide fragment. This Tyr^1 – Phe^4 tetrapeptide is well-known in the art to be required for opioid

activity (Lipkowski et al. J. Med. Chem. 29:1222-1225, 1986. First paragraph of the Introduction; Form PTO-1449 of May 17, 2002). Furthermore, claim 63 recites "adjuvant," and, therefore, reads on a vaccine. Applicants have provided no guidance or working examples of how to use any OM/SPM chimera in a pharmaceutical composition as a vaccine, nor have they taught for what diseases or conditions this vaccine is to be used. In addition, it is not predictable to one of ordinary skill in the art how to use these chimeras as a vaccine.

Additionally, the breadth of claims 60, 61, 101 and 102 regarding OM/SPM chimeras which comprise an unspecified number of "non-natural amino acids" is excessive. While the specification enables chimeras comprising the mu opioid receptor binding moieties of Table 1 and the SP receptor binding moieties of Table 4, of which either or both comprise at least one "D-amino acid," the specification does not provide any guidance or working examples of these chimeras which comprise "non-natural amino acids" other than D-amino acids, or how to make functional chimeras which comprise non-natural amino acids for use in pharmaceutical compositions. Though claims 61 and 102 recite that the peptide comprises at least one D-amino acid, the peptide may still comprise "non-natural amino acids" other than D-amino acids. Furthermore, it is unpredictable to the artisan how to make functional chimeras for use in pharmaceutical compositions other than by using the peptide moieties disclosed in Tables 1 and 4 of the specification.

Therefore, in summary, the breadth of the claims is excessive regarding chimeras comprising any and all mu opioid receptor binding moieties and SP receptor agonist binding moieties other than those based on the endogenous peptides listed in Tables 1 and 4 of the specification, as well as any derivatives thereof. The breadth of the claims is also excessive regarding all opioid/SP chimeras which comprise an unspecified number of "non-natural amino acids." Furthermore, there is no guidance or working examples of "derivatives" of these peptides other than those disclosed in Tables 1 and 4 of the specification, of how to produce functional derivatives of these peptides for pharmaceutical use, how to use these compositions, including vaccines, or how to produce functional peptides which comprise "non-natural amino acids" other than D-amino acids. These factors, along with the lack of predictability to the artisan how to make functional (i.e. therapeutically active) chimeras for use in pharmaceutical compositions other than by using the peptides disclosed in Tables 1 and 4 of the specification, lead the Examiner to hold that undue experimentation is necessary to practice the invention as claimed. Claims 2, 26-30, 46-48, 50-52, 54, 55, 67-71, 87-89, 91-93, 95 and 96 are rejected since they depend from rejected base claims. It is believed that all pertinent arguments have been addressed.

6. Claim Rejections - 35 USC § 112, first paragraph – written description

A. New claims 25-33, 45-52, 54, 55, 57, 60, 61, 66-74, 86-93, 95, 96, 98, 101 and 102 are rejected under 35 USC 112, first paragraph for the reasons already of record on pages 3-4 of the Office Action dated 12/17/01 regarding previous claims 1-17. Claims 3-17 have been cancelled. The rejection of the term "fragment" has been withdrawn in view of Applicants' arguments on pages 21 and 22 of the response dated 3/15/02, as well as pages 9, line 8 to page 11, line 12 of the specification, which define "fragments." Though Applicants do not specifically address the term "derivative," Applicants argue that the specification teaches that the opioid receptor binding moiety should preferably be N-terminal, and end with a Tyr residue, and that the SP receptor binding moiety should preferably be C-terminal and have a protected COOH moiety. Applicants further provide one embodiment of a novel chimeric peptide as claimed, SEQ ID NO:42 as well as examples of opioid and SP binding moieties satisfying these characteristics (Tables 1-4, and Figures 2 and 3, though Tables 2 and 3 are drawn to non-elected species).

These arguments have been considered, but are not deemed persuasive. Applicants do disclose that the OM be N-terminal, and end with a Tyr residue, and that the SP receptor binding moiety should preferably be C-terminal and have a protected COOH moiety. They also disclose SEQ ID NO:42 and examples of opioid and SP binding moieties satisfying these characteristics. However, Applicants have only disclosed these characteristics regarding endogenous mu opioid peptides as well as the endogenous ligand, SP, and, therefore, only provided adequate written description regarding these two classes of receptor binding moieties. Furthermore, Applicants define "derivatives" of a peptide as a sequence of at least 4 amino acids which specifically recognize an epitope. However, Applicants do not provide any description as to what this epitope is, if this epitope is the same in all of these "derivatives," or if it is a randomly chosen epitope not related to peptide function. Applicants further define these derivatives as a molecule other than full-length and which may be as little as 30% identical to (i) an amino acid sequence of identical size, or (ii) when compared to an aligned sequence, or (iii) when the encoding nucleic acid is capable of hybridizing under even non-stringent conditions to the nucleotide sequences encoding these aforementioned peptides and amino acid sequences (page 10, line 26 to page 11, line 12 of the specification). Furthermore, page 11, lines 13-23 define derivatives as containing various additions, deletions and substitutions to the original peptide and which result in "functionally equivalent molecules." However, it is not understood what this "function" is, or which amino acid residues are critical to maintain this function. Therefore, one of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus of claimed "derivatives." Thus,

Applicant was not in possession of the claimed genus at the time the invention was made. It is believed that all pertinent arguments have been addressed.

7. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 24-33, 45-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1, 25, 31-33, 45, 49, 57, 66, 72-74, 86, 90 and 98 are confusing since the metes and bounds of "N-terminal" and "C-terminal" are not known. These terms can be defined as a peptide encompassing anywhere from as little as one amino acid of the N- and C-terminus, respectively, up to the entire length of the peptide, excluding only the last C- or N-terminal amino acid residue, respectively. Claims 2, 24, 26-30, 46-48, 50-52, 54, 55, 60-65, 67-71, 87-89, 91-93, 95, 96, 101 and 102 are also rejected since they depend from these rejected claims.

B. Claim 1, 45 and 86 are confusing since it is not clear if the binding moiety binds a SP receptor agonist, or if the SP receptor binding moiety is an agonist. Claims 2, 24-33, 46-52, 54, 55, 57, 60-74, 87-93, 95, 96, 98, 101 and 102 are also rejected since they depend from rejected claims.

C. Claims 24, 25, 27, 65, 66 and 68 are confusing since they recite the phrase "the mu receptor." It appears that there is only one mu opioid receptor, or that the claims are drawn to a specific mu opioid receptor. It is suggested that the claims be amended to recite "a mu receptor." Again, Applicants are reminded that non-elected subject matter must be removed from the claims. Claims 26, 45-52, 54, 55, 86-93, 95, 96 are also rejected since they depend from these rejected claims.

D. Claims 31, 33, 49, 72, 74 and 90 are confusing since they recite an improper Markush Group. It is not clear if the receptor binding moieties consist of *every* SEQ ID NO recited in the claim (e.g. every SEQ ID NO:1-11), or if the moieties are selected from one sequence selected from "the group consisting of." It is recommended that the claims be amended, as appropriate, to recite, for example, "the group consisting of any one of SEQ ID NO:1 to 11."

E. Claims 60 and 101 are confusing since it is not understood if the term "non-natural" refers to an amino acid which exists in nature, but does not naturally occur in the claimed peptide, or if the amino acid is one that is man-made (i.e. not found in nature). Claims 61 and 102 are also rejected since they depend from claims 60 and 101, respectively.

F. Claim 63 is confusing since the metes and bounds of the term "adjuvant" are not known. The Merriam-Webster Dictionary defines "adjuvant" as 1: serving to aid or contribute, or 2: assisting in the prevention, amelioration, or cure of disease (http://m-w.com/). In this case, since the specification does not disclose the use of the claimed pharmaceutical composition as a vaccine, it is not clear to the Examiner which meaning of the term is intended; common usage in the art would include either a substance which would serve to augment an immune response, or alternatively an additional active ingredient, and if so, what. If the intent is that the adjuvant is to be a substance which would augment an immune response, then issues are raised under 35 USC 112, first paragraph; see rejection above.

8. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. The rejection of previous claims 1-17 under 35 USC 103(a) as being unpatentable over Kream et al. in view of Cavagnero et al. and further in view of Lappi et al. for the reasons of record on pages 4-5 of the Office Action dated 12/17/01, has been withdrawn in view of Applicants' arguments that it would not have been obvious for one of ordinary skill in the art to "try" to combine these teachings because there was no suggestion to combine these references, nor was there any expectation of success in the combination in order to achieve the claimed invention, for the reasons provided by Applicants on pages 22-25 of the response dated 3/15/02.

B. Claims 1, 2, 24-33, 45-49, 57, 60-74, 86-90, 98, 101 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments, p 113-118, 1994 – on Form PTO-1449 of Paper No. 15) in view of Lipkowski et al. (J. Med. Chem. 29:1222-1225, 1986 – on Form PTO-1449 of Paper No. 15), further in view of Lipkowski et

al. (Life Sci. 33:141-144, 1983 – on Form PTO-1449 of Paper No. 14), further in view of Maszczynska et al. (Let. Pep. Sci. 5:395-398, 1998), and further in view of Smith et al. (U.S. Patent 6,310,072).

Claim 1 recites a chimeric peptide comprising an N-terminal opioid receptor binding moiety and a C-terminal Substance P receptor agonist binding moiety. Claim 2 recites that the peptide induces analgesia when administered to a mammal. Claims 24 and 27 recite that the opioid receptor binding moiety binds to a mu opioid receptor. Claim 25 recites that the opioid moiety comprises a ligand, an N-terminal derivative, or an N-terminal fragment thereof. Claims 26 and 28 recite that the opioid moiety is an agonist. Claims 29 and 30 recite that the opioid moiety is a free amine including, Tyr. Claims 31-33 recite that the opioid moiety is endomorphin 1, endomorphin 2, SEQ ID NO:3, or a fragment, or derivative thereof. Claim 45 recites that the SP moiety is SP, a C-terminal SP fragment, or a C-terminal SP derivative. Claims 46-48 recite that the –COOH moiety of the SP moiety is protected by amidation (i.e.. NH_2). Claim 49 recites that the SP moiety is SEQ ID NO:21. Claim 57 recites that the chimera comprises an opioid moiety which is endomorphin 1, 2, N-terminal fragments, or N-terminal derivatives thereof and an SP moiety which is SP, a C-terminal fragment, or a C-terminal derivative thereof. Claims 60 and 61 recite that the peptide comprises at least one non-natural amino acid, including a D-amino acid. Claims 62, 64-74, 86-90, 98, 101 and 102 recite pharmaceutical compositions comprising the chimeras of claims 1, 2, 24-33, 45-49 and 57. Claim 62 recites that this composition comprise a pharmaceutically acceptable diluent. Claim 63 recites the composition of claim 62 further comprising an adjuvant.

Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments) teach the production of a chimeric peptide comprising the N-terminal fragment of a casomorphin, Tyr-Pro-D-Phe-Phe, (an opioid binding moiety. Table 1 of the specification) with the C-terminal fragment of an SP *antagonist*, to produce the chimera, Tyr-Pro-D-Phe-Phe-D-Phe-D-Trp-Met-NH_2 (Abstract). This N-terminal fragment of casomorphin comprises an N-terminal Tyr (free amine), and this "Tyr-Pro-Phe-Phe" tetrapeptide agonist (i.e. ligand) is 100% identical to that of SEQ ID NO:3 of the present invention, except for the substitution of the "D-amino acid," D-Phe. Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments) also teach that this peptide chimera induces analgesia when administered to mice when administered in a pharmaceutically acceptable diluent (i.e. NaCl; Figure 3; page 114, paragraphs 1 and 3 under "Materials and Methods"). Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments) do not specifically teach a chimera which comprises the N-terminal fragment of an OM with an SPM *agonist*. However, they do teach the Substance P receptor agonist binding moiety, SP, which is 100% identical to SEQ ID NO:21 of the present invention, and that the

amidated (i.e. protected, Met-NH_2) C-terminal fragment of the agonist, SP, itself, Phe-Phe-Gly-Leu-Met-NH_2, is biologically active (Figures 1 and 2) in producing contractions in the guinea pig ileum.

In addition, Lipkowski et al. (Life Sci.) do teach chimeras in which the N-terminal part of the SP receptor agonist binding moiety, SP, was replaced by an enkephalin (opioid receptor binding moiety) active fragment, which comprises Tyr^1 – Phe^4, and that this peptide demonstrated naloxone-reversible opiate activity in various in vivo tests (Abstract). In fact, Lipkowski et al. (J. Med. Chem.) teach that most endogenous opioid peptide analogs, such as endomorphin 1 and endomorphin 2, contain an N-terminal tetrapeptide fragment and that this tetrapeptide, Tyr^1 – Phe^4, is an important requirement for opioid activity (first paragraph of the Introduction).

However, none of Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments), Lipkowski et al. (J. Med. Chem.), or Lipkowski et al. (Life Sci.) teach a pharmaceutical composition comprising an adjuvant. Since the definition of "adjuvant" is not clear for the reasons in the above rejection of claim 63 under 35 USC 112, second paragraph, this term is being defined as something which is "serving to aid or contribute" to producing analgesia, or "assisting in the...amelioration...of disease," wherein the disease in pain. Therefore, this does not necessarily read on a vaccine, as discussed in the above scope of enablement rejection under 35 USC 112, first paragraph, but reads on another analgesic compound which can be co-administered with the claimed chimera. Smith et al. do teach pharmaceutical compositions comprising an adjuvant since they teach a mu opioid agonist co-administered with a kappa opioid agonist. In this situation, the kappa opioid agonist, oxycodone, would be acting as an adjuvant since it would be "serving to aid or contribute" to the effects of the mu agonist, morphine (Examples I and II). Smith et al. teach a pharmaceutically acceptable composition comprising these agonists (Abstract) and pharmaceutically acceptable diluents (e.g. syrup, vegetable oil, oil-in-water; column 8, lines 49 – column 9, line 24).

Therefore, given the teachings of Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments), who teach a chimeric OM/SPM antagonist peptide, as well as C-terminal fragments of the agonist, SP, Lipkowski et al. (Life Sci.), who teach chimeras in which the N-terminal part of the SP receptor agonist binding moiety, SP, was replaced by an enkephalin, Lipkowski et al. (J. Med. Chem.), who teach that most endogenous opioid peptide analogs, such as endomorphin 1 and endomorphin 2, contain an N-terminal tetrapeptide fragment and that this tetrapeptide, Tyr^1 – Phe^4, is an important requirement for opioid activity, and Smith et al. who teach opioid pharmaceutical compositions comprising adjuvants, it would have been obvious to one of ordinary skill in the art at the time of the invention to have produced peptide chimeras comprising the N-terminus of any mu opioid receptor

binding moieties which comprises the tetrapeptide, $Tyr^1 - Phe^4$, including endomorphin 1 or endomorphin 2 (SEQ ID NO:3 of the present invention), and the C-terminus of an SP receptor agonist binding moiety (i.e. a C-terminal fragment of SEQ ID NO:21 of the claimed invention). One of ordinary skill in the art would have been motivated to combine the teachings of Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments), Lipkowski et al. (Life Sci.), Lipkowski et al. (J. Med. Chem.) and Smith et al. (U.S. Patent No. 6,310,072) in view of Maszczynska et al. (Let. Pep. Sci.) who teach that SP is capable of reinforcing spinal morphine (a mu opioid agonist binding moiety) analgesia as seen in the tail-flick test (Abstract; page 396, left column, first full paragraph). This pharmacological effect was blocked by administration of naloxone, demonstrating that this potentiated analgesic effect is mediated by activation of opioid expressing neurons. Maszczynska et al. (Let. Pep. Sci.) also teach that findings of SP reinforcement of morphine analgesia indicates the complementary, and potential value, of further attention to combination pharmacotherapies applying SP and opioids in concert (Conclusion).

Furthermore, though neither Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments), nor Lipkowski et al. (Life Sci.) teach a chimera comprising endomorphin 1 or endomorphin 2, it would have been obvious to one of ordinary skill in the art at the time of the present invention to have substituted the N-terminal portion of SP with the $Tyr^1 - Phe^4$ tetrapeptide of any endogenous mu opioid receptor binding moiety, including that of either endomorphin 1 or endomorphin 2 since, as taught by Lipkowski et al. (J. Med. Chem.), this tetrapeptide, $Tyr^1 - Phe^4$, is an important requirement for opioid activity (first paragraph of the Introduction).

One of ordinary skill in the art would have also had a reasonable expectation of success in producing chimeras comprising the N-terminus of an OM and the C-terminus of an SPM since techniques to produce chimeras were well-known and highly successful in the art at the time of the present invention, as evident from the above teachings by both Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments) and Lipkowski et al. (Life Sci.) who teach that OM/SPM peptide chimeras already exist and that these chimeras are capable of acting via opioid receptor-expressing neurons to potentiate opioid analgesia. The artisan would have also been motivated to have used the adjuvant of Smith et al. along with these chimeric peptides to further increase their analgesic potential since Smith et al. demonstrate the advantage of coadministering opioid binding moieties (i.e. an opioid and an "adjuvant" opioid – Figures 2A and 2B of U.S. Patent 6.310,072).

Finally, the use of opioid drugs, including opioid peptides, has been accompanied by side-effects such as dependence, tolerance and respiratory depression (Lipkowski et al. in β-Casomorphins and Related Peptides: Recent Developments). Therefore, to limit the potential side-effects of opioid drugs,

and to stimulate "as many receptors involved in pain transmission and modulation as possible," chimeras between opioids and non-opioid peptides should be considered in the search for potential analgesic drugs (page 114, last paragraph of Introduction). These combined teachings will allow the artisan to further elucidate the mechanism of action of both the opioid and SP receptor systems, as well as to identify and use other OM/SPM chimeras for the induction of analgesia, as taught in the prior art.

C. Claims 50-52, 54, 55, 91-93, 95 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments, p 113-118, 1994 – on Form PTO-1449 of Paper No. 15) in view of Lipkowski et al. (J. Med. Chem. 29:1222-1225, 1986 – on Form PTO-1449 of Paper No. 15), further in view of Lipkowski et al. (Life Sci. 33:141-144, 1983 – on Form PTO-1449 of Paper No. 14), further in view of Maszczynska et al. (Let. Pep. Sci. 5:395-398, 1998) and further in view of Watson et al. (Eur. J. Pharmacol. 87(1) :77-84, 1983).

Claims 50-52, 54 and 55 recite that the –COOH moiety of the SP moiety is protected by esterification (e.g. methyl or ethyl esters). Claims 91-93, 95 and 96 recite pharmaceutical compositions comprising the chimeras of claims 50-52, 54 and 55. The teachings of Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments), Lipkowski et al. (J. Med. Chem.), Lipkowski et al. (Life Sci.) and Maszczynska et al. (Let. Pep. Sci.) are provided in the above rejection under 35 USC 103(a). However, none of Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments), Lipkowski et al. (J. Med. Chem.), Lipkowski et al. (Life Sci.) and Maszczynska et al. (Let. Pep. Sci.) teach that the –COOH moiety of the SP moiety is protected by esterification (e.g. methyl or ethyl esters). However, Watson et al. do teach that C-terminal alkyl esters of SP (Abstract; Tables I and II) exhibit a higher degree of selectivity to a particular SP receptor subtype, which would allow one of ordinary skill in the art to differentiate between two or more SP receptors.

Although the reference is silent to the use of alkyl esters to protect the COOH terminus of a peptide, the teachings of Watson et al. would lead the artisan to make the claimed structures. The property of "protection" is inherent in these peptides. In fact, the use of methyl and other esters to protect the C-terminus of various amino acids in a peptide is also taught by Lipkowski et al. (J. Med. Chem., page 1223, second paragraph under "Design Rationale and Chemistry"). Therefore, one of ordinary skill in the art would have been motivated to have esterified the C-terminal amino acid of the chimeras of the present invention in order to either protect them, as taught by Lipkowski et al. (J. Med. Chem.), or to improve receptor selectivity, as taught by Watson et al. The artisan would have also had a reasonable expectation of success in producing these "esterified" chimeras since techniques for esterifying peptides, including

SP, are well-known and highly successful in the art, as evidenced by their production by Lipkowski et al. and Watson et al.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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June 03, 2002